REMARKS/ARGUMENT

Status of Claims

Claims 16, 21-65 have been canceled.

Claims 1-15 and 17-20 and 66-80 stand rejected.

Claims 1, 2, 4-15, 17-20, 66-72, 75, 78 and 80 are currently amended.

New claims 81-90 have been added.

Claims 1-15, 17-20 and 66-90 are currently pending.

Objection to the Specification - Priority

In the Office Action dated January 30, 2003, it is said that the earliest priority date of the instant application is that of U.S. Provisional Patent Application No. 60/229,071, August 30, 2000. Applicant respectfully traverses and asserts that the present application is entitled to a priority date at least as early as the filing date of U.S. Provisional Patent Application No. 60/208,348, May 31, 2000. Claim 1 is currently amended to omit the recitation that the immunoglobulin inhibition is reversed by binding steroid hormone to a steroid hormone receptor that is active for promoting cell growth. At least claims 1, 6, 76 and new claims 83-85 are fully supported in the specification of 60/208,348. See 60/208,348 at page 1, third paragraph; page 3, fourth paragraph; page 4, last paragraph; page 5, last paragraph; page 7, fourth paragraph; for example.

Rejections Under 35 U.S.C. § 112, Second Paragraph.

In the Office Action, claims 5, 12 and 20 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to claim 5, it is said that the terms "significant increase" and "significant lack of increase" render the claims indefinite, and that "the specification provides no standard for determining the metes and bounds of 'significant increase' in a cell population apart from a 'significant increase in cell population doublings'." Claim 5 is currently amended to recite "cell population doublings."

With respect to claim 12, it is said that a step linking the method objective to loss or reduction of immunoglobulin inhibitor is lacking. Claim 12 is currently amended to recite the active method step of using the detection from the prior detecting step to predict susceptibility of the subject to development of breast cancer wherein a detected loss or impairment of inhibition indicates greater risk of development of breast cancer.

With respect to claim 20, it is said in the Office Action that there are no teachings in the prior art or the specification to indicate the structure or function for an Estrogen Receptor gamma. Claim 20 is currently amended to omit reference to detecting ERγ (estrogen receptor gamma) and to instead recite detecting high-affinity estrogen binding activity wherein E2 binding affinity is greater than that of ERα (estrogen receptor alpha) or ERβ (estrogen receptor beta). As currently amended, claim 20 also requires using that detection to determine that the presence or absence of the high-affinity estrogen binding activity indicates whether the cell is estrogen dependent for growth. By this amendment, Applicant does not disclaim that the high affinity estrogen binding activity identified in the specification (*e.g.*, in Examples 18 and 19, especially paragraphs 405 and 417) reflects a previously unrecognized estrogen receptor denoted in the specification as ERγ (estrogen receptor gamma).

Rejections Under 35 U.S.C. § 112, First Paragraph.

Written Description

Claims 1-15, 17-19 and 66-80 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. In the Office Action it is said that "applicant contends that no protein constituent described by other(s) which inhibits mucosal cell growth possesses the same master switch property as applicants immunoglobulin inhibitors and none are steroid hormone reversible in the same way as Applicants...," and it is also said that "applicant has not described the structural and functional attributes of the immunoglobulin inhibitors which would render them distinguishable (from) other immunoglobulins that were not part of the claimed invention. The Office Action takes the position that the claims "encompass a genus of immunoglobulin inhibitors, a genus of poly-Ig receptor and Fc receptors, and a genus of steroid hormones and steroid hormone receptors that are not described in the art."

In reply, Applicant respectfully traverses this misinterpretation of Applicant's previous argument. It is respectfully submitted that such interpretation is inconsistent with the teachings of the specification (see paragraphs 18, 379, 390 - 392, and elsewhere in the specification). Applicant's argument in the previous Response referred to the components isolated from blood serum which are said to inhibit estrogen dependent cell growth, including the inhibitors described by Sonnenschein *et al.* and Tanji *et al.* For example, Sonnenschein *et al.* ultimately identified their serum borne inhibitor as albumen. Tanji *et al.* partially characterized their serum-derived component(s) by functional properties that differ from those described by Applicant. Of the known inhibitors of estrogen dependent cell growth, none has been identified as an immunoglobulin of the IgA, IgM, IgG1 or IgG2 classes of the secretory immune system, much less dimeric/polymeric IgA or polymeric IgM. This is not an assertion

that the immunoglobulin inhibitors employed in the claimed methods must be other than active forms of the naturally occurring secretory immunoglobulins (*e.g.*, dimeric/polymeric IgA, polymeric IgM, IgG1 and IgG2), as taught in the specification. Thus, the functional and structural attributes of immunoglobulin inhibitors, and of an Fc receptor and a poly-Ig receptor which would bind the immunoglobulin inhibitors, are adequately defined in the specification and the prior art.

With respect to claims 20 and 77-79, which depend therefrom, it is said in the Office Action (p. 7) that "when given the broadest reasonable interpretation in light of newly added claim 79, claims 20 and 77-79 are dependent upon the identity of a steroid hormone receptor that has not been disclosed, as the gamma isoform of the Estrogen Receptor is not recognized in the art or described in the specification." As currently amended, these claims now omit the term "ERγ" and instead recite the high-affinity estrogen binding activity in which E_2 binding affinity is greater than that of either ERα or ERβ.

Applicant is also currently amending claims 1, 7 - 10, 12 - 15, 17 - 19, 68, 71, 72, 75 and 80 to omit reference to "binding steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth." Instead, these claims recite that "inhibition of steroid hormone responsive cell growth is capable of being reversed by said steroid hormone" or "wherein immunoglobulin regulation comprises steroid hormone reversible inhibition of steroid hormone responsive mucosal epithelial cell growth by IgG1 or IgG2." (claim 71).

New Matter

In support of the rejection of claim 66 on the ground of new matter, it is stated in the Office Action that the specification teaches using the students t-test, wherein a value of $p<0.05$ is significant, only in the context of cell population doublings. Claim 66 is currently amended to recite "cell population doublings," and thus avoids the present ground of rejection.

Claims 77 - 79 also stand rejected in the Office Action as being drawn to new matter. It is said that "[t]he specification teaches immunocytes localized in mucosal epithelial tissues but does not contemplate increasing the level of immunocytes in a therapeutic method." Applicants respectfully submit that paragraph 560 teaches

> IgA and IgM will be administered to young female animals initially to diminish the effects of carcinogens. These studies will then be followed by oral "immunizations' to increase the natural levels of immunoglobulin secreting B-cells within the mammary tissue. (Claim 77).

Also, see paragraphs 481, 490, 551, 554 and 567 of the specification, for example.

In is also said in the Office Action that claims 78 and 79 are not supported in the original specification. While it is acknowledged by the Office that the specification contemplates tamoxifen as a therapeutic, the Office Action suggests that it does not contemplate the identification of tamoxifen in an assay for an antagonist of ER gamma. Applicant respectfully submits, however, that claims 78 and 79 are supported in Examples 19, 20, and 32, at paragraph 510, for example, where it is taught that

> The action of tamoxifen as an antagonist of the ERγ will find use in the evaluation and treatment of estrogen responsive cancers. Better treatment regimes employing tamoxifen can be devised because the clinician can now be better informed about the possible effects of the drug.

As discussed above with respect to claim 20, references in the specification to a deduced ERγ reflect the observed high-affinity estrogen binding activity which is greater than that of ERα or ERβ. Applicant's disclosure demonstrates estrogen reversibility of the inhibition (of steroid hormone responsive mucosal epithelial cell growth by immunoglobulin inhibitors) at physiological levels of the hormone (*i.e.*, picomolar concentrations). See paragraphs 259, 291, 398, 399 and Figs. 92, 97 and 100, for example. In Example 7, and elsewhere in the specification, it is described how to assay for estrogen-like activity of substances of interest. From the teachings in Applicant's disclosure, one of ordinary skill in the art at the time Applicants' invention was made would recognize how to test a substance, including tamoxifen, for any antagonistic effect on the high-affinity estrogen binding activity.

With respect to alleles and defective gene sequences, it is said in the Office Action that "[o]ne of skill in the art would conclude that applicant was not in possession of the claimed genus because the known genes encoding the poly Ig receptor and the Fc receptor are not representative of the variants of the claimed genus." Applicant respectfully submits that, in light of the foregoing argument regarding the identity of the immunoglobulin inhibitors, the known poly-Ig receptor gene and the known Fc receptor gene are indeed representative of the variants described in claims 10, 11, 69 and 80. Claim 10 is drawn to a method comprising steps that will lead to detection of a variant poly-Ig receptor gene. It is not a claim to a variant gene, per se. Similarly, claim 80 is drawn to a method of detecting a variant Fc receptor gene. Claims 11 and 69 are drawn to methods of detecting expression of a defective mediator of immunoglobulin inhibition by expressing the genes that are detected according to the methods of claims 10 and 80, respectively. Applicant respectfully requests withdrawal of the rejection of these claims.

Enablement

Claims 1-7, 9-15, 17-19, 66-76 and 80 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In support of this rejection, the Office Action states that "[t]he specification provides no guidance on the structure or function of the disclosed immunoglobulin inhibitors which would differentiate them from the prior art immunoglobulin inhibitors. Thus the instant specification doesn't teach one of skill in the art how to make the immunoglobulin inhibitors of the instant invention." Applicant submits, however, that this ground of rejection rests on the same misunderstanding discussed above regarding identity of the "immunoglobulin inhibitors." Applicant does not assert that the claimed immunoglobulin inhibitors must be other than active forms of naturally occurring secretory immunoglobulins (*e.g.*, dimeric/polymeric IgA, polymeric IgM, IgG1 and IgG2).

Garde et al. and *Gomez et al.* support Applicant's position that there are known techniques and adequate skill in the art to permit the artisan, when given Applicant's disclosure, to determine without undue experimentation the relevant ranges or levels of secretory immunoglobulins that are indicative of normal individual(s) or of individuals who have, or are at risk of developing, a steroid hormone responsive cancer of a mucosal epithelial tissue. Such tests could readily take into account any age related, diurnal or circadian, or other variations, without undue experimentation. It is noteworthy that *Garde et al.* reports (at p. 554, col. 2) that no seasonal effects were observed for IgA, and suggests that one way to reduce the biological variation (of a parameter) is to restrict sample collection to specific hours of the day (p. 558, cols. 1 and 2). In the absence of Applicant's disclosure, however, the artisan would not necessarily measure the active forms of the secretory immunoglobulins (*i.e.*, active for inhibiting steroid hormone reversible steroid hormone responsive growth of a mucosal epithelial cell). Additionally, he or she would have no idea to use the dimeric/polymeric IgA measurements as an indicator of whether a steroid hormone responsive mucosal epithelial tissue exposed to the IgA is contacted by insufficient immunoglobulin inhibitor to suppress steroid hormone responsive cell growth. Instead, he or she would be led to measure IgA level(s) merely as an indicator of the effect of sex steroid hormones on IgA secretion (*Gomez et al.*), or to use IgA levels as a general marker of the immune system (*Garde et al.*, p. 555, col. 2) or as a tumor marker (*Garde et al.* p. 320, col. 2). Applicant respectfully submits that given Applicant's disclosure and the knowledge of one of ordinary skill in the art at the time Applicants' invention was made, one would be able to use the claimed methods.

Rejection Under 35 U.S.C. § 102(b).

Claim 20 is also rejected under 35 U.S.C. § 102(b) as being anticipated by *Becchis et al.* In support of this rejection, the Office Action states that *Becchis et al.* disclose that estrogen positive and/or progesterone receptor negative status of breast tumors is indicative of a better prognosis of breast cancer patients, thus fulfilling the specific embodiment of claim 20. Applicant respectfully submits that as currently amended on other grounds, claim 20 requires detecting a high-affinity estrogen binding activity having a greater E_2 binding affinity than that of ERα or ERβ. *Becchis et al.* does not teach any ER activity other than that of the conventional ER. For at least this reason, claim 20 distinguishes over *Becchis et al.*

Additional Amendments

Any current amendments to the claims that are not specifically discussed above, are made for reasons other than patentability. For example, to improve the claim form, to use terminology that is believed to be more consistent with wording in the specification or with other claims, or to ensure coverage of specific embodiments to which Applicant is entitled. New claims 82-85 are drawn to embodiments that are fully supported in the '348 priority document. New claim 89 contains subject matter that was split out of claim 2 in order to help focus any issues that potentially remain in controversy with respect to sources of body fluids or secretions used according to claim 1.

EXAMINER INTERVIEW SUMMARY

Applicant gratefully acknowledges the telephone interview with Examiner Karen A. Canella on November 19, 2003. The specific issues, claims and prior art that were discussed in detail are set out in the ***Applicant Initiated Interview Request Form*** which was filed on November 10, 2003. Proposed amendments to the claims were discussed which may obviate at least some of the outstanding grounds of rejection. The general result of the interview was that Applicant would amend the claims and submit argument consistent with the discussions, and would file a ***Request for Continued Examination***, whereupon the rejections would be reconsidered by the Examiner.

Conclusion

Applicant believes that this is a full and complete response to each rejection, objection and requirement. If any item has been overlooked, the opportunity to supplement this response is respectfully requested. Applicant may have at times referred to claim limitations in shorthand fashion,

or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other arguments with respect to patentability which have yet to be raised, but which may be raised in the future.

Applicant respectfully requests reconsideration of this application and allowance of all claims. If any issues remain in controversy, Applicant respectfully requests a telephonic Examiner Interview to facilitate the resolution of such matters. Should any fees have been inadvertently omitted, or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Deposit Account Number 03-2769 of Conley Rose, P.C., Houston, Texas, and consider this a petition for any necessary extension of time.

Respectfully submitted,

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